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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,978	06/27/2006	Claudio Soto-Jara	281278US0PCT	9597

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.  
1940 DUKE STREET  
ALEXANDRIA, VA 22314

EXAMINER
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HORNING, MICHELLE S

ART UNIT	PAPER NUMBER
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1648

NOTIFICATION DATE	DELIVERY MODE
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01/27/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/560,978	<b>Applicant(s)</b> SOTO-JARA ET AL.	
	<b>Examiner</b> MICHELLE HORNING	<b>Art Unit</b> 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 03 November 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 15-22, 27 and 29-59 is/are pending in the application.
- 4a) Of the above claim(s) 16, 27, 33 and 51-57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 15, 17-20, 30, 35, 38, 40, 43-47, 50, 58 and 59 is/are rejected.
- 7) ☒ Claim(s) 21, 22, 29, 31, 32, 34, 36, 37, 39, 41, 42, 48 and 49 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

This action is responsive to communication filed 11/3/2008. Any rejection not reiterated herein has been withdrawn.

#### ***Claim Rejections - 35 USC § 112-NECESSITATED BY AMENDMENT (NEW)***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.** The claims are drawn to a “general diagnosis” and it is not clear what the term means. Note that because “general diagnosis” is not a term used in the art, it cannot be determined whether there is implicit support for the term in the instant specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

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application was filed, had possession of the claimed invention. The term “general diagnosis” or a similar term was not provided in the specification as filed.

***Claim Rejections - 35 USC § 103-MAINTAINED***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

*Given the arguments for the rejections are similar, they are addressed together below.*

**Claims 15, 17-20, 30, 35, 38, 40, 43-45 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Soto et al (2002), Baumann et al (2000) and Huang et al (2001) in further view of Clavey et al (1991, cited).**

Soto et al disclose the method of cyclic amplification of protein misfolding (PMCA), including the amplification of infectious TSE protein (see whole document). The authors note that such amplification "offers the possibility of amplifying the amount of PrP<sup>Sc</sup> in a sample, making its detection by existing methods easier" (see page 391). Page 392 provides that PMCA requires a PrP<sup>C</sup> substrate in high molar excess for conversion. The authors discuss how such a method of amplification combined with sensitive detection methods would allow for the early diagnosis of TSE for both sample and living animals and people (see page 393). This publication does not teach the use of ApoE or its fragments.

Baumann et al provide evidence that ApoE enhances the amyloidogenicity of PrP proteins (see whole document and page 78). Figure 4 demonstrates this enhancement of PrP and beta-amyloid proteins by way of a ThT assay of formed amyloid fibrils. Of note, the authors provide the following statement: "deposits in various amyloidoses and prion diseases include both biochemically and immunohistochemically detectable amounts of apoE. Thus the molecular interaction of apoE seems not to be specific for AD but more a common characteristic in the development of other amyloidoses as well" (see Discussion, page 82). The author dubbed apoE as a "universal pathological chaperone" and noted that each amyloidogenic fragment tested (prion and beta-amyloid) demonstrated that apoE is mediated through only one common binding site (see page 82).

Huang et al disclose that apoE fragments induce neurofibrillary tangles in neurons (see whole document). More specifically, the authors conclude that carboxyl-

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terminal-truncated forms of apoE induce such tangles compared to other truncated apoE in neuronal cells.

It would have been obvious to one of ordinary skill in the art to combine the teachings above in order to perform a method of PrPsc detection. One would have been motivated to amplify PrPsc (as taught by Soto et al) and further enhance such the PrPc-PrPsc transition by providing ApoE or its fragments (as taught by Baumann et al or by Huang et al) in order to make its detection easier. Further, the ordinary artisan would have been motivated to screen for drugs which would inhibit the PrPc-PrPsc transition using this method. There would have been a reasonable expectation of success given the methods are well characterized by the prior art, including the successes of the references above. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Lastly, Clavey et al provides that apoE binds LDL receptors. Thus, claims 30, 35, 40 and 50 are rejected given this binding is inherent.

**Claims 20, 44, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Soto et al (2002), Baumann et al (2000) and Huang et al (2001) and Naslavsky et al (1997) in further view of Clavey et al (1991, cited).**

Claims 20 and 44 are rejected as the teachings apply above. Soto et al, Baumann et al, Huang et al and Clavey et al do not teach using lipid rafts from N2a cells as a source of normal PrPc and substrate (see claims 46 and 47).

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Naslavsky et al characterize the detergent-insoluble complexes containing the PrPc and its scrapie isoforms in N2a cells (see whole document). The authors provide that PrPc is localized to rafts and its attachment to rafts is essential for the efficient conversion of PrPc into PrPsc (see Discussion). Lastly, the authors provide an extraction procedure for the isolation and characterization of either the PrPc or the PrPsc raft (whole document). Thus, it would have been obvious to combine the teachings above to perform a screening assay for modulatory compounds using lipid rafts from N2a cells. One would have been motivated to do so given the extraction procedure for the isolation of the PrPc raft is well characterized by Naslavsky et al. There would have been a reasonable expectation of success given the authors provided a successful method. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

Applicant's arguments filed 11/3/2008 have been fully considered but they are not persuasive. Applicant argues that each reference fails to teach that ApoE promotes PrPc to PrPsc transition. This is incorrect. The basis of the Baumann teachings is that ApoE induces and accelerates the beta-sheet conformation in prions and amyloid beta-peptides (see Introduction). Further, the instant specification provides the following in paragraph 14 regarding the teachings by Baumann: "Apolipoprotein E was found to recognize a shared structural motif of amyloids and prion which, after induction, can accelerate the adoption of a beta-sheet conformation (Baumann et al., 2000)." For clarity, the structure of the infectious PrPsc disclosed by the prior art is provided in

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paragraph 4 by the instant specification: "Chemical differences have not been detected to distinguish these two PrP isoforms and the conversion seems to involve a conformational change whereby the alpha-helical content of the normal protein diminishes and the amount of beta-sheet increases (Pan et al., 1993). The structural changes are followed by alterations in the biochemical properties: PrPc is soluble in non-denaturing detergents, PrPsc is insoluble; PrPc is readily digested by proteases (also called protease sensitive prion protein) while PrPsc is partially resistant, resulting in the formation of a N-terminally truncated fragment known as PrPc is (protease resistant prion protein) (Cohen et al., 1998)." Thus, Baumann discloses that ApoE accelerates the beta-sheet conformation of prions, the scrapie conformation, and this is further evidenced by the specification.

### ***Allowable Matter***

The following claims are allowable but are objected to for depending on rejected claims: claims 21, 22, 29, 31, 32, 34, 36, 37, 39, 41, 42, 48 and 49. Note that the prior art discloses that ApoE accelerates a PrPc to PrPsc transition but does not disclose that ApoB causes this transition. Also, the sequences of ApoB and E submitted by the Applicant show they are structurally distinct in terms of length and sequence.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).



A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/  
Examiner, Art Unit 1648  
/Bruce Campell/  
Supervisory Patent Examiner, Art Unit 1648